DE GRUYTER
OPEN
Romanian Journal of Rhinology, Vol. 7, No. 25, January-March 2017 DOI: 10.1515/rjr-2017-0004

ORIGINAL STUDY

Cystic fibrosis - general review on sinonasal complications and case report

Claudiu Manea[1,2,3], Alina Diaconescu[1]
[1]ENT&HNS Department, "Sfanta Maria" Hospital, Bucharest, Romania
[2]CESITO Center, "Sfanta Maria" Hospital, Bucharest, Romania
[3]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

An irreversible disease, cystic fibrosis (CF), is responsible for affecting multiple organ systems containing epithelia. It is well known that the sinonasal disease caused by CF has consequences for the incidence of the lower airway exacerbations, as well as affecting the quality of life of those patients. This review provides an update by evaluating the available literature regarding pathogenesis, management and treatment of cystic fibrosis patients. To gain a better view of the disease and obtain a higher life expectancy, further studies are needed.
KEYWORDS: cystic fibrosis, sinonasal disease, paranasal sinuses, nasal polyposis

INTRODUCTION

Cystic fibrosis is a life-limiting, irreversible disorder with autosomal-recessive transmission, and it has effects on multiple organ systems containing epithelia. It is estimated to have an incidence of 1 in 2000 up to 1 in 6000 births in Caucasians[1]. The advancement in medicine permitted many improvements in the survival of these patients with median life expectancy of approximately 40 years[2].

The genetic basis of this disorder is a malfunction of the CF transmembrane conductance regulator (CFTR), an anion located on the membrane of the respiratory and exocrine glandular epithelium. The secretion of the glands is more viscous and causes obstructions that lead to inflammation and tissue damage. After affecting the pancreatic exocrine function (malnutrition and poor growth), the biliary duct, the male reproductive system, sweat glands, the most important cause of death is obstructive lung disease. Sinonasal disease as a consequence of increased viscosity of the mucus is an important factor of the patient's evolution by being a continuous source of recurrent infections. The epidemiology of the cystic fibrosis involves mainly upper and lower airways in 90-100% of CF patients[3]. Almost 80% of the patients with CF have nasal obstruction, more than 50% have rhinorrhea and headache, and 25% have anosmia[4]. The prevalence of nasal polyposis in patients with CF is from 6% to 48%; it increases during adolescence[5].

Nowadays, the diagnosis is prenatal or the disease is discovered after newborn screening. Prenatal diagnosis is an invasive test from fetal genetic material and carries a small risk of miscarriage[6]. Newborn screening, if positive, will lead to the confirmation of the diagnosis - the sweat test (high salt levels confirm a diagnosis of CF).

The treatment is mainly based on preventing any upper or lower airways infection and having a diet that limits the malabsorption to minimum.

This article discusses a clinical case of nasal polyposis in a cystic fibrosis patient treated in "Sfanta Maria" ENT Department in November 2016. The particularities of the diagnosis and treatment are presented together with a short literature review regarding the sinonasal complication of the disease.

Corresponding author: Claudiu Manea, MD, PhD, Associate Professor, ENT&HNS Department, CESITO Center, "Sfanta Maria" Hospital, 37-39 Ion Mihalache Blvd., District 1, Bucharest, Romania
e-mail: cmmanea@yahoo.com

SINONASAL DISEASE IN CYSTIC FIBROSIS PATIENTS

PATHOGENESIS

Patients with CF have a particularity in the viscoelastic properties of the mucus, an impaired mucociliary clearance, added to the abnormal chloride conductance. Viscosity in mucus is 30-60 times higher than in patients without CF[7]. The sinus ostia are obstructed and the lacks of ventilation and of oxygen associated with edema are the main factors for bacterial overgrowth. The most common bacteria isolated from sinus cultures of the patients with cystic fibrosis are *Staphylococcus aureus, P. aeruginosa, Burkholderia cepacia, Escherichia coli, Acinetobacter species, Haemophilus influenzae, Stenotrophomonas maltophilia,* anaerobes and *Streptococci*[8-11]. Sinuses serve as a reservoir for recurrent lung infection for CF patients, fact confirmed by Godot et al[12].

Antimicrobial resistance, a consequence of multiple antibiotics exposures, has become an important aspect of the treatment and an important cause of morbidity. Those who underwent inhalation treatment with many steroids and antibiotics are also the best candidates for fungus pulmonary infection, mainly with Candida species.

Nasal polyposis is associated with cystic fibrosis in a proportion of 7-48%[13], mediated by neutrophilic Th1-mediated inflammation, different from eosinophilic Th2-mediated inflammation and polyposis that appear in non-CF patients[14].

The anatomy is changed and hypoplasia of the paranasal sinuses is a characteristic of the disease well described in literature. The most valid theory blames ongoing mucosal inflammation as the cause for poor pneumatization of head bones. Also, genotype influences the development of paranasal sinuses[15-18]. The fact that patients with F508 del mutation have been proven to have underdevelopment of the sinuses compared to other mutations suggests that CFTR may be an important contributor to sinus development[19].

CLINICAL MANIFESTATIONS

Rhinosinusitis, when present, frequently includes: rhinorrhea, nasal obstruction, anosmia, mouth breathing, facial pain, voice changes, headache and halitosis.

Nasal polyposis is associated with nasal obstruction, anosmia, mouth breathing, thick anterior and posterior discharge, followed by facial deformation, hypertelorism due to the widening of the nasal bridge.

DIAGNOSIS

The history of the patient and clinical examination must always be associated with imaging of paranasal sinuses of CF patients. Anterior and posterior rhinoscopy show single or multiple, grey, pale masses from the middle meatus and prolapsing into the nasal cavity, associated with abundant and thick anterior and posterior rhinorrhea.

CT scans of paranasal sinuses of cystic fibrosis patients show reduced size of the maxillary sinuses and frontal or sphenoidal hypoplasia, which are very specific features. The anterior ethmoid cells grow more slowly than the posterior ones, causing an inversion of their relationship[4]. Frontal sinus agenesis and maxillo-ehtmoidal sinuses opacification greater than 76% have been proposed as pathognomonic criteria for CF[20].

MANAGEMENT

Treatment of the disease is mainly systemic; the patients are treated medically before considering surgical treatment. The scope of the treatment is to reduce the risk of pulmonary infections by reducing the size of nasal polyps, relieve nasal obstruction, restore sinus normal drainage.

Clinical management

The medical management of the disease includes systemic and topical medication. Dornase Alfa, AINS, oral antibiotics associated with nasal irrigations, topical steroids and topical antibiotics form the most efficient treatment for these patients, as listed below:

1) Dornase Alfa. It is a medication that reduces DNA fragment length and reduces mucus viscosity of CF patients. It also slows the rate of the decline of lung function in patients older than 5 years[21-23].
2) Ibuprofen. Its use and efficiency was shown in 2007 by Konstan et al.[24] and by Lindstrom et al.[25] by reducing the progression of the pulmonary disease and the size of nasal polyps.
3) Macrolide antibiotics. Clarithromycin and azithromycin are well known for their anti- inflammatory properties, but their main role in this disease treatment is the decrease of IL-8 produced by nasal cells[26], thus reducing the sinus inflammation. The dosage and scheduling is still a matter of discussion[27].
4) Nasal saline irrigations. Hypotonic and isotonic saline irrigations are the best way to mechanically clean the crusts and hypertonic saline irrigations decongest by osmosis. There is no meta-analysis of CF patients, but the recommendation is made from studies of non-CF patients where nasal saline irrigations have been proven to help relief nasal obstruction and clean the nasal mucosa.
5) Topical steroids. Even if topical steroids are effective on eosinophilic nasal polyposis, it has been noted that they have an important role on neutrophilic polyposis in CF patients.
6) Topical antibiotics. Even if Lim et al.[28] showed in 2008 that there is no sufficient proof to justify the use of topical antibiotics in chronic rhinosinusitis

patients, in CF patients, prophylaxis with tobramycin is an important step of the treatment. After surgery, nebulization with gentamicin or tobramycin is recommended to prevent bacteria from the sinus populate the lungs.

7) New therapies have been targeting the CFTR channel. Ivancaftor by potentiating the mutant CFTR existing on the membrane, Lumacaftor by improving delivery of the CFTR to the plasma and Ataluren, which induces translational read-through of nonsense mutations. All these three drugs are in phase 3 of testing[29,30].

Surgical management

After following a medical treatment and the symptoms of rhinosinusitis or nasal polyposis persist, the CF patients receive the recommendation for surgery. There are studies presenting the effect of sinus surgery as a very important one for these patients: a better control of the pulmonary infection as a consequence of limiting the sinus bacteria reservoir[31].

The nature of the disease predisposes the patients to repeated interventions, so it is very important for them to take into consideration if the benefits of a surgical treatment are higher than its risks. Standard FESS includes frontal sinusotomy, sphenoidectomy, anterior and posterior ethmoidectomy, maxillary antrostomy. Polypectomy is the least invasive part of the treatment and, if possible, after medical management. Pulmonary exacerbation after FESS is prevented by medical treatment guided by prophylaxis of bacteria and fungi infections. There are studies such as Rowe-Jonce and Mackay that report a rate of revision of the patients with nasal polyposis and cystic fibrosis of 50% in the next 18-24 months[32]. Most pediatric patients who undergo endoscopic surgery appear to have improved symptom profile, but the imagistic score rarely modifies after it.

CASE REPORT

A 9-year-old boy was admitted in our ENT Department for bilateral nasal obstruction, anterior and posterior thick rhinorrhea that occurred 6 months previously. His medical records showed that the patient was previously evaluated in another ENT Clinic and diagnosed with polyposis (multiple polypectomy - 2015;2014;2013). The patient was diagnosed with CF when he was 4 months old and has been treated since then according to a multidisciplinary protocol. The clinical examination showed grey pale polyploid masses which filled the entire left and right nasal fossae, nasal mucosa with high-density mucous secretions in both nasal cavities and hypertrophic inferior turbinates.

Native and contrast-enhanced CT scan described fronto-maxillary-ethmoid rhinosinusitis and severe bilateral hypertrophy of the nasal mucosa with polypoid component in the left choana (Figure 1).

Our decission considering the recurrence and all other complications of the disease was to perform endoscopic surgery. Intraoperatively, a grey pale polypoid mass, arising from the middle meatus into the nasal cavity was found in the left and right nasal fossae (Figure 2). Polypectomy was performed, with bilateral maxillary antrostomy (Figure 3) and anterior ethmoidectomy on the right side and complete ethmoidectomy on the left side.

Before the surgical procedure, the patient underwent a medical treatment including topical tobramy-

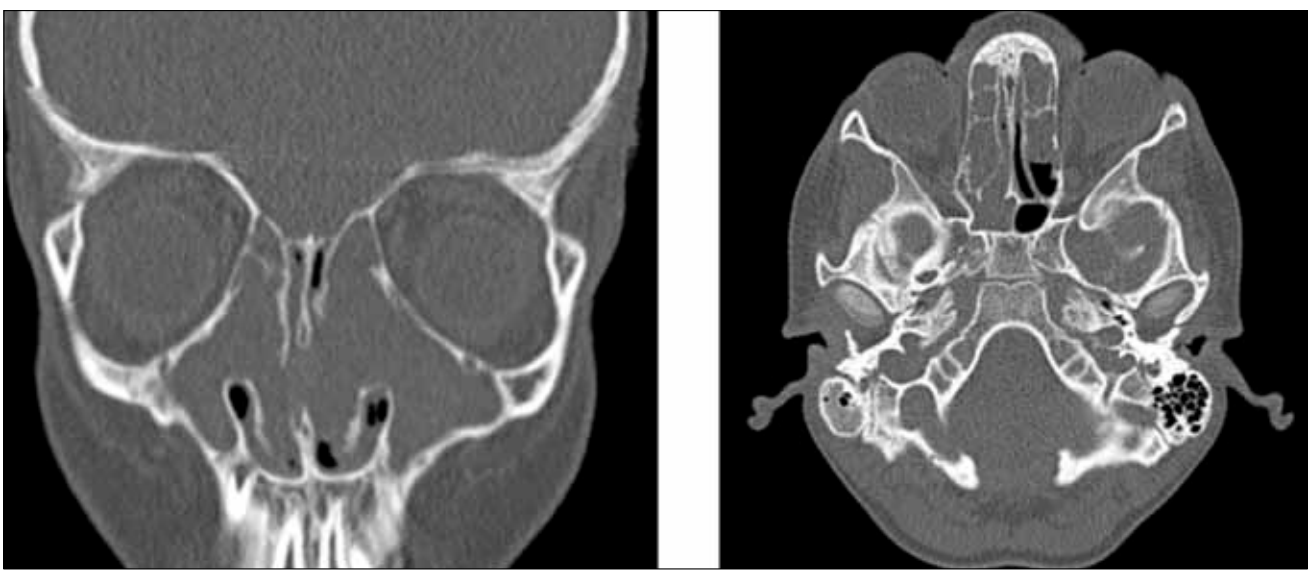

Figure 1 Opacification of maxillary sinuses with erosion of the nasal septum, complete opacification of the antero-posterior ethmoidal cells on the left side and anterior ethmoidal cells on the right side.

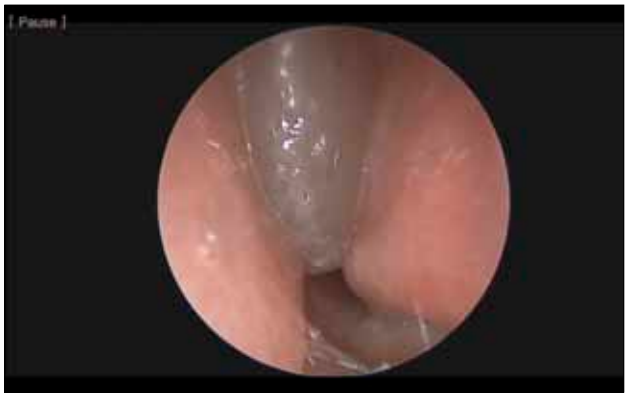

Figure 2 Intraoperative aspect of nasal polyposis arising from the middle meatus to the nasal cavity.

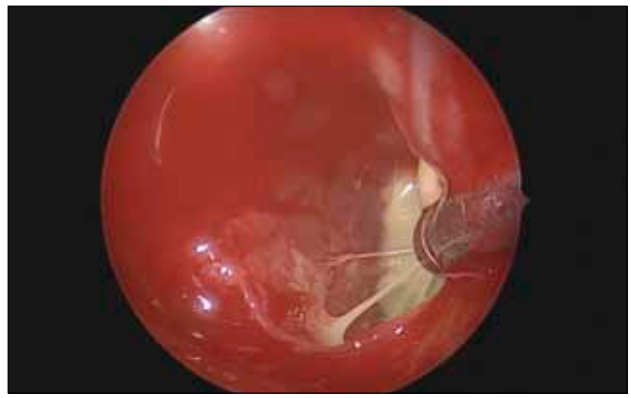

Figure 3 Intraoperative aspect-endosinusal view (maxillary sinus).

cin, Pulmozyme, Alfa dornase, a prophilactic dose of Fluconazole, Cefotaxime and Vancomycin.

The histopathological examination reconfirmed nasal polyposis.

The post-operative evolution was good, without complications, but the result of the sinus cultures came back positive with presence of S. aureus with multiple drug resistance. The recommendation in this case was inhaled gentamicin, twice a day, 14 days.

CONCLUSIONS

Being a chronic disease, cystic fibrosis impairs the patients' quality of life in many ways. The sinonasal disease is an important treatment target and requires surveillance and compliance.

The main scope is to reduce the recurrence of the infections, to reduce the symptoms of the nasal disease and have a higher life expectancy of these patients with minimum surgical intervention.

Conflict of interest: The authors have no conflict of interest.

Contribution of authors: All authors have equally contributed to this work.

REFERENCES

1. Rowe S.M., Miller S., Sorscher E.J. - Cystic fibrosis. N Engl J Med., 2005;352(19):1992-2001.
2. Cystic Fibrosis Foundation Patient Registry 2011 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation, 2012.
3. Oomen K.P., April M.M. - Sinonasal manifestations in Cystic fibrosis. Int J Otolaryngol., 2012;2012:789572. doi: 10.1155/2012/789572. Epub 2012 Aug 5.
4. Brihaye P., Jorissen M., Clement P.A. - Chronic rinosinusistis in cystic fibrosis (mucoviscidosis). Acta Otorhinolaryngol Belg., 1997;51(4):323-337.
5. Steinke J.W., Payne S.C., Chen P.G., Negri J., Stelow E.B., Borish L. - Etiology of nasal polyps in cystic fiborisis: not a unimodal disease. Ann Otol Rhinol Laryngol., 2012;121(9):579-586.
6. Tabor A., Alfirevic Z. - Update on procedure-related risks for prenatal diagnosis techniques. Fetal Diagn Ther., 2010;27(1):1–7. doi: 10.1159/000271995. Epub 2009 Dec 24.
7. Gentile V.G., Isaacson G. - Patterns of sinusitis in cystic fibrosis. Laryngoscope, 1996;106(8):1005-1009.
8. Shapiro E.D., Milmoe G.J., Wald E.R., Rodnan J.B., Bowen A.D. - Bacteriology of the maxillary sinuses in patients with cystic fibrosis. J Infect Dis., 1982;146(5):589–593.
9. Halvorson D.J., Dupree J.R., Porubsky E.S. - Management of chronic sinusitis in the adult cystic fibrosis patient. Ann Otol Rhinol Laryngol., 1998;107(11 Pt 1):946–952.
10. Mak G.K., Henig N.R. - Sinus disease in cystic fibrosis. Clin Rev Allergy Immunol., 2001;21(1):51–63.
11. Moss R.B., King V.V. - Management of sinusitis in cystic fibrosis by endoscopic surgery and serial antimicrobial lavage. Reduction in recurrence requiring surgery. Arch Otolaryngol Head Neck Surg., 1995;121(5):566–572.
12. Godoy J.M., Godoy A.N., Ribalta G., Largo I. - Bacterial pattern in chronic sinusitis and cystic fibrosis. Otolaryngol Head Neck Surg., 2011;145(4):673–676. doi: 10.1177/0194599811407279. Epub 2011 Apr 26.
13. Robertson J.M., Friedman E.M., Rubin B.K. - Nasal and sinus disease in cystic fibrosis. Paediatr Respir Rev., 2008;9(3):213–219. doi: 10.1019/j.prrv.2008.04.003. Epub 2008 Jul 31.
14. Van Zele T., Claeys S., Gevaert P., Van Maele G., Holtappels G., Van Cauwenberger P., Bachert C. - Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy, 2006;61(11):1280–1289.
15. Welsh M.J., Smith A.E. - Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. Cell, 1993;73(7):1251–1254.
16. Accurso F.J., Rowe S.M., Clancy J.P., et al. - Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. N Engl J Med., 2010;363(21):1991–2003. doi: 10.1056/NEJmoa0909825.
17. Gan K.H., Veeze H.J., van den Ouweland A., et al. - A cystic fibrosis mutation associated with mild lung disease. N Engl J Med., 1995;333:95–99.
18. Haardt M., Benharouga M., Lechardeur D., Kartner N., Lukacs G.L. - C-terminal truncations destabilize the cystic fibrosis transmembrane conductance regulator without impairing its biogenesis. A novel class of mutation. J Biol Chem., 1999;274(31):21873–21877.
19. Woodworth B.A., Ahn C., Flume P.A., Schlosser R.J. - The delta F508 mutation in cystic fibrosis and impact on sinus development. Am J Rhinol., 2007;21(1):122–127.
20. Nishioka G.J., Cook P.R., McKinsey J.P., Rodriguez F.J. - Paranasal sinus computed tomography scan findings in patients with cystic fibrosis. Otolayngol Head Neck Surg., 1996:114(3):394-399.
21. Fuchs H.J., Borowitz D.S., Christiansen D.H., Morris E.M., Nash M.L., Ramsey B.W., Rosenstein B.J., Smith A.L., Wohl M.E. for the Pulmozyme

Study Group - Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. N Engl J Med., 1994;331:637–642.

22. Quan J.M., Tiddens H.A., Sy J.P., McKenzie S.G., Montgomery M.D., Robinson P.J., Wohl M.E., Konstan M.W., Pulmozyme Early Intervention Trial Study Group - A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. J Pediatr., 2001;139(6):813–820.
23. Harms H.K., Matouk E., Tournier G., von der Hardt H., Weller P.H., Romano L., Heijerman H.G., FitzGerald M.X., Richard D., Strandvik B., Kolbe J., Kraemer R., Michalsen H. - Multicenter, open-label study of recombinant human DNase in cystic fibrosis patients with moderate lung disease. DNase International Study Group. Pediatr Pulmonol., 1998;26(3):155–161.
24. Konstan M.W., Schluchter M.D., Xue W., Davis P.B. - Clinical use of Ibuprofen is associated with slower FEV1 decline in children with cystic fibrosis. Am J Respir Crit Care Med., 2007;176(11):1084–1089.
25. Lindstrom D.R., Conley S.F., Splaingard M.L., Gershan W.M. - Ibuprofen therapy and nasal polyposis in cystic fibrosis patients. J Otolaryngol., 2007;36(5):309–314.
26. Suzuki H., Shimomura A., Ikeda K., Furukawa M., Oshima T., Takasaka T. - Inhibitory effect of macrolides on interleukin-8 secretion from cultured human nasal epithelial cells. Laryngoscope, 1997;107(12 Pt 1):1661–1666.
27. Saiman L., Marshall B.C., Mayer-Hamblett N., Burns J.L., Quittner A.L., Cibene D.A., Coquillette S., Fieberg A.Y., Accurso F.J., Campbell P.W. 3rd; Macrolide Study Group. - Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: A randomized controlled trial. JAMA, 2003;290(13):1749–1756.
28. Lim M., Citardi M.J., Leong J.L. - Topical antimicrobials in the management of chronic rhinosinusitis: a systematic review. Am J Rhinol., 2008;22(4):381–389.
29. Kim Chiaw P., Eckford P.D., Bear C.E. - Insights into the mechanisms underlying CFTR channel activity, the molecular basis for cystic fibrosis and strategies for therapy. Essays Biochem., 2011;50(1):233–248. doi: 10.1042/bse0500233.
30. Pettit R.S. - Cystic fibrosis transmembrane conductance regulator-modifying medications: the future of cystic fibrosis treatment. Ann Pharmacother., 2012;46(7-8):1065–1075. doi: 10.1345/aph.1R076. Epub 2012 Jun 26.
31. Lewiston N., King V., Umetsu D., Starnes V., Marshall S., Kramer M., Theodore J. - Cystic fibrosis patients who have undergone heart-lung transplantation benefit from maxillary sinus antrostomy and repeated sinus lavage. Transplant Proc., 1991;23(1 Pt 2):1207–1208.
32. Rowe-Jones J.M., Mackay I.S. - Endoscopic sinus surgery in the treatment of cystic fibrosis with nasal polyposis. Laryngoscope, 1996;106(12 Pt 1):1540–1544.